

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ALACHLOR

SB 950-071, Tolerance # 00249

Nov. 10, 1986

Revised 3/16/87, 6/5/87, 3/17/89, 3/23/90

I. DATA GAP STATUS

Combined rat: No data gap, possible adverse effect (onco and chronic)

Chronic rat: (see combined rat, above)

Chronic dog: No data gap, no adverse effect

Oncogenicity rat: (see combined rat, above)

Oncogenicity mouse: No data gap, possible adverse effect

Reproduction rat: No data gap, no adverse effect

Teratology rat: No data gap, no adverse effect

Page 2

Teratology rabbit: No data gap, no adverse effect

Gene mutation: No data gap, no adverse effect

Chromosome: No data gap, no adverse effect

DNA damage: No data gap, possible adverse effect

Neurotoxicity: not required at this time

-----**Note, Toxicology**
one-liners are attached

In document/record number headings of 1-liners below:

** indicates acceptable study

Bold face indicates possible adverse effect

All records on file with CDFA as of 1/23/89 have been reconciled. Record numbers covered range from 0 to 067756 (Document No. 249-132), as well as some records in the >900000 series.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED

RAT

The following key study (Biodynamics, 11/3/81; Vols. 21-25) was originally classified as an oncogenicity study (Christopher, 4/15/85). The 3/16/87 Summary of Toxicology Data reclassified the study as a "combined" study, considering the additional information from two Monsanto studies (Vols. 56-57 and Vols. 59-60). All three of these study "one-liners" are grouped together as of the March, 1989 review, since they are interrelated. C. Aldous, 3/10/89.

****021 - 025 029655-56, 031965-67**, (old record No. on J. Christopher's review was 963637). "A chronic feeding study of Alachlor in rats." Bio/dynamics, 11/3/81, (study designation BDN-77-421). Alachlor, 92.6%. Test article used during the first year was stabilized with 0.5% epichlorohydrin (see Vol. 20, part 3, p. 8). Epichlorohydrin was subsequently removed from tech. alachlor used in this study and from all alachlor produced by the Monsanto, or used by Monsanto for subsequent studies. Monsanto studies in CDFA Vols. 056-057 and 059-060 were considered in chronic toxicity/oncogenicity evaluation. Study 021:029655 used 0, 14, 42, and 126 mg/kg/day in diet, 50/sex/group. No definitive NOEL was found in study 021:029655 (mild degree of uveal degeneration syndrome in eyes of 2 males at 14 mg/kg/day: apparent mild periportal hepatocyte hypertrophy and centrilobular hepatocyte necrosis at 14 mg/kg/day). A "non-neoplasia effects" NOEL of 2.5 mg/kg/day derives from study 059:006445. **Possible adverse effects** include: **malignant stomach tumors** (carcinomas, sarcomas, and "mixed"; marked incidence in M and F at 126 mg/kg/day, plus one in F at 42 mg/kg/day); **nasal turbinate tumors** (generally adenomas; dose-related in M and F at 42 to 126 mg/kg/day); **thyroid follicular tumors** (generally adenomas, definitive in 126 mg/kg/day M, weak indications in 42-126 mg/kg/day F); **uveal degeneration syndrome** (M and F, definitive and dose-related at 42 and 126 mg/kg/day). In addition, possible treatment effects include low incidence of rare brain tumors (ependymoma

at 42-126 mg/kg/day in F and 126 mg/kg/day in M; one oligodendroglioma in a 126 mg/kg/day M); also non-statistically significant increases in "nodular hyperplasia" or hepatocellular adenomas in 126 mg/kg/day M and F, respectively. These and other major findings are tabulated and discussed in 3/10/89 review. **Acceptable.** J. Christopher, 4/12/85, C. Aldous, 3/10/89.

097 048630 Monsanto response to the 4/12/85 CDFA review of the 11/3/81 Bio/dynamics study (Vol. 21-25). Statistical data were provided on major oncogenicity and chronic effects in the study. The new information indicates that there is no NOEL for chronic effects in this study due to liver necrosis at all treatment levels, statistically significant even at the lowest level. The discussion in the CDFA Supplementary Worksheet for this response indicates that follow-up studies allow establishment of an LEL for chronic effects of 15 mg/kg/day, and a NOEL of 2.5 mg/kg/day. [Note: the 3/16/87 Summary of Toxicology Data incorrectly considered the overall NOEL for rat chronic toxicity to be 15 mg/kg/day. This could not be correct, considering that in study 059:006445, 15 mg/kg/day was clearly an effect level: there were non-neoplastic and neoplastic lesions in the nasal turbinates in that study]. C. Aldous, 10/28/86, 3/10/89.

020 029650 Summary of 1981 Biodynamics study reported in vols. 021-025.

029 963640 Summary of in-life physical observations for rat combined study: Vols. 021 - 025.

010 963663 Final ophthalmological exam reports for rat combined study: Vols. 021 - 025.

020 29646 Supplement to rat combined study above (Vols. 021 - 025, report located in Tab 3, p. 5). Brief summary relating to tumor findings, as part of Monsanto's assessment of oncogenic risk.

056-057 006442-43 "Special Chronic Study of Alachlor Administered in Feed to Long-Evans rats". Monsanto Project No. ML-80-224, 4/16/84. (A follow-up to primary Biodynamics study BDN-77-421, 021:029655). A single-dose study with technical alachlor (94.1%) administered at

126 mg/kg/day in diet to Long-Evans rats, 100/sex. Design involved three treatment groups: a 25-month continuous dosing group; a recovery group involving 5-6 month dosing, followed by control diet up to 25-month sacrifice; and a group given continuous treatment up to sacrifice at 8 months. **Possible adverse effects**, previously identified in study 021:029655, were confirmed in this study. These included uveal degeneration syndrome, which was found to be irreversible, and discontinuance of treatment did not necessarily arrest progression of symptoms. Nasal turbinate adenomas or adenocarcinomas were found in M and F lifetime treated rats, and in the recovery study. Gastric carcinomas, sarcomas, or mixed tumors were found in 3/68 M and in 19/30 F in lifetime exposure groups, but not in recovery rats. Lifetime treatment elicited thyroid follicular tumors in males only; however in the recovery group, these tumors were not demonstrably elevated in either sex. Bone marrow myelocytic hyperplasia and urinary bladder epithelial hyperplasia also appeared to be increased due to treatment. J. Christopher, 4/15/85; C. Aldous 3/14/89 (see also March 1989 "Supplemental Information Worksheet" on collective rat studies related to 021:029655).

097 048632 Response to "UNACCEPTABLE" classification of study: 056:006442, Monsanto, 4/12/84. The study is so classified because it cannot independently fill a data gap, and not as an indication of failure to fulfill its intended function. This study contributes meaningfully toward filling the data gap for rat chronic and oncogenicity data requirements, which are now considered filled. C. Aldous, 10/27/86).

074 017655 Addendum to 4/16/84 Monsanto study (ML-80-224). Clarification regarding tumors in or adjacent to and affecting the brain in study described above: Vols. 056 and 057.

****059, 060 006445-46** "Chronic Study of Alachlor Administered in Feed to Long-Evans rats". Monsanto, St. Louis, MO. 2/27/84. (Supplemental to primary study by Biodynamics, 021:029655). Alachlor, tech., (no epichlorohydrin in this tech.). 50/sex given 0, 0.5, 2.5, or 15 mg/kg/day in diet: NOEL for chronic tox = 2.5 mg/kg/day (nasal submucosal gland hyperplasia at 15 mg/kg/day (M & F). Significant increases in nasal epithelial adenomas in M and F at 15 mg/kg/day. One stomach adenocarcinoma (rare tumor) in 2.5 mg/kg/day male attributed by

investigators to test article, considering results of other studies. ACCEPTABLE, useful data.
J. Christopher, 4/15/85.

097 048631 Response to two issues noted by John P. Christopher in his 4/15/85 review of above study (059:006445, Monsanto, 2/27/84). Registrant noted reason for selection of Long-Evans strain is because the 1981 Biodynamics study (Vols. 021-025) used the same strain. Registrant acknowledged that hematology/clinical chemistry assays were not as frequent as suggested in current guidelines, however that the 1981 study had already adequately assessed these parameters. This reviewer considers John P. Christopher's concerns to be adequately addressed, and the report should be considered ACCEPTABLE and a significant contribution toward filling the rat chronic/oncogenicity data gap. (C. Aldous, 10/27/86).

011 046912 "Herbicide, Chronic and Delayed Effects Studies: two-year chronic oral toxicity study with Lasso Technical in albino rats". (Rec. # 963611 given on worksheet. The latter "Rec. #" was not applied uniquely to this study, but was used repeatedly for various types of studies within this review. This study is reported on pp. 14-16 of section C.) IBT, 9/16/77 (BTL-72-7 study ruled invalid by EPA.). Summary only. Lasso, tech. 0, 100, 300, and 1000 ppm in diet of "albino" rats. No tumorigenicity nor other significant effects on microscopic evaluation. UNACCEPTABLE, NOT upgradeable. (EPA invalid, dose levels clearly too low.) J. Christopher, 4/4/85.

020 029648 (another summary of 011:046912; see above).

105 050238 Information submitted by Monsanto to FIFRA Science Advisory Panel in response to EPA classification of alachlor as a "B2" oncogen. This is not a study, but rather a risk assessment document, and has been examined as such by CDFA Health Assessment Group. No review is necessary by Data Review Group (C. Aldous, 3/16/89).

112 055472 "Statement of Thomas W. Fuhremann" [Toxicology - Alachlor Review Board]. An interpretative summary of alachlor data representing several study types. No new data presented. This statement is primarily of interest in risk assessment. Representative topics

include apparent strain specificity of uveal degeneration syndrome, and apparent thresholds for thyroid and other tumors. No Data Review Group review is appropriate. C. Aldous, 3/16/89.

DOG

103 049227 "Chronic study of alachlor administered by gelatin capsule to dogs" Environmental Health Lab (Monsanto), 11/16/84. Alachlor, tech. 0, 1.0, 3.0, and 10.0 mg/kg/day. NOEL = 1.0 mg/kg/day (based primarily on slight, dose-related incidence of hemosiderosis or excess hemosiderin in kidney, liver, and spleen; also on modest increases in gastro-intestinal findings such as diarrhea, mucus stool, and other stool abnormalities: all of these findings predominantly in males). Mild anemia and mild liver toxicity indicated at 10 mg/kg/day, particularly in males. **Acceptable. Study was previously considered to represent "possible adverse effects", to flag a comparatively low NOEL (even though there was not remarkable toxicity at the LEL). The "possible adverse effects" flag is no longer used to advise Health Assessment Group of low NOELs, hence the flag is removed as of 3/16/89. (C. Aldous, 11/3/86, 6/5/87, 3/16/89).

011 029618 "Summary of Toxicology Studies Conducted on Lasso Herbicide, Chronic and Delayed Effects Studies: Two-Year chronic oral toxicity study with Lasso Technical in beagle dogs". (Rec. # 963611 given on worksheet. The latter "Rec. #" was not applied uniquely to this study, but was used repeatedly for various types of studies within this review. This study is reported on p. 14 of section C.) IBT, 6/10/74 (BTL-72-8). Summary only. Lasso, tech. This IBT study ruled invalid by EPA. 0, 100, 300, and 1000 ppm in diet of beagles. No significant adverse effects noted. UNACCEPTABLE, NOT UPGRADEABLE. (EPA invalid). John P. Christopher, 4/4/85.

ONCOGENICITY**RAT**

(See Combined, rat)

MOUSE

****014, 015 963643 and 046246** "Eighteen Month Chronic Feeding Study of Alachlor in mice". Bio/dynamics, 6/18/81 (Study No. BD-77-423). Alachlor tech., 92.6% (with 0.5% epichlorohydrin as stabilizer for first 11 months, final 7 months without epichlorohydrin. 0, 26, 78, and 260 mg/kg/day in diet, 50/sex/group. Apparent chronic toxicity NOEL = 26 mg/kg/day (increased liver/BW and kidney/BW ratios in males at 78 mg/kg/day and above. Slight decrease F survival at 260 mg/kg/day.) Increases in lung adenomas and carcinomas of F at 260 mg/kg/day and increases in liver adenomas and carcinomas of M at 260 mg/kg/day. Originally classified as UNACCEPTABLE (confounding effect of epichlorohydrin, lack of stability of test article during the time period following removal of epichlorohydrin from the technical, many missing tissues in animals dying on study, missing BW and food consumption individual data, inadequate mortality data evaluation [needs K-M curves]). A rebuttal (see 098:048633, below) allowed an upgrade to ACCEPTABLE status for this study. A subsequent rebuttal plus new information (114:060100 and 125:061246, see one-liners below) prompted removal of liver tumors as an apparent treatment effect, however there is insufficient information to change CDFA conclusion that lung tumors constitute a "possible adverse effect". J. Christopher, 4/12/85, C. Aldous, 10/28/86, 3/16/89 (worksheets bear record numbers 060100 and 061246).

098 048633 Monsanto response to John P. Christopher review of study: 014:963643, Bio/dynamics, 6/18/81 (Study No. BD-77-423). Some additional data have been provided in this submission. Some rebuttals were submitted in response to concerns that Dr. Christopher had indicated as reasons for not accepting the study. Some items for which additional information could have been provided were not further elucidated, the registrant citing adequacy of data as previously provided. This reviewer (CNA) recommends considering this study as ACCEPTABLE for the mouse oncogenicity data requirement. C. Aldous, 10/28/86.

114 060100 (relates to primary study, 014:963643). "Witness statement of R. Harold Grice" (representing Monsanto Canada at Alachlor cancellation hearings). No date, but prior to 7/23/87. Statement addresses the lung tumor (alveologenic adenoma and carcinoma) potential of alachlor with respect to the above 18-month mouse study. Arguments were (1) These are common

tumor types with unusually low incidence in concurrent control females. (2) A true treatment effect should have shown a typical distribution pattern over time, with increasing incidence over the last months of the study. (3) True treatment effects should include multiplicity of tumors, which was not observed here. (4) Compounds which cause lung tumors generally are not sex-specific. (5) There were no associated increases in tumor incidence, and particularly, no increase in tumor progression, such as from adenomas to carcinomas. (6) General provisions used by regulatory agencies to evaluate oncogenicity studies were not applied to this study. In addition to these major points, Bio/dynamics laboratory historical control data were provided. CDFA acknowledged the usefulness of this evaluation and requests additional information about the historical data (see review for details). C. Aldous, 3/16/89.

125 061246 (Rebuttal to mouse oncogenicity study review for record 014:963643, study by Bio/dynamics, dated 6/18/81). Date of this rebuttal: 8/26/87. Registrant presented a case that there is insufficient evidence to conclude that liver tumors were treatment-related in males. All other commentary related to female lung tumor data. A statement by Haseman (1984) was quoted, indicating that common tumors should be considered treatment-related only if significant at the $p < 0.01$ level. The EPA Science Advisory Panel concluded that the mouse was negative for oncogenicity. BIBRA reviewers concluded similarly; they noted, among other things, that more lung tumors should have been observed in high dose female survivors to term if alachlor were oncogenic in lungs of females. CDFA Action: re-examination of the data finds **insufficient reason to consider liver tumors a treatment effect**. There is **insufficient information to make a final decision about lung tumors**: CDFA will consider the above comments when re-examining the mouse lung tumor data, on receipt of the historical control data requested in the CDFA review of Dr. Grice's comments (Record 114:060100). C. Aldous, 3/16/89.

020 029647 Summary of 014:963643, see one-liner, above.

029 963644 Summary of in-life physical observations for 014:963643.

075 017656 Addendum to pathology report of study 014:963643.

017 963638 Summary of 014:963643, see one-liner, above.

011 29619 "Summary of Toxicology Studies Conducted on Lasso Herbicide, Chronic and Delayed Effects Studies: Eighteen month mouse carcinogenic study with Lasso Technical in albino mice". (Rec. # 963611 given on worksheet. The latter "Rec. #" was not applied uniquely to this study, but was used repeatedly for various types of studies within this review. This study is reported on p. 13 of section C.) IBT, 7/17/74 (BTL-72-9A) Summary only. Lasso, tech. An IBT study ruled invalid by EPA. 0, 100, 300, and 1000 ppm in diet of "albino" mice. No significant adverse effects noted. UNACCEPTABLE, NOT UPGRADEABLE. (IBT invalid, dose levels apparently too low.) J. Christopher, 4/4/85.

020 029649 1-page summary of 011:029619.

008 029591 (Original Rec. No. was 963641). 7/8/80. Appendix to invalid IBT mouse oncogenicity study (IBT 621 1182) with histological evaluation of eyes. No adverse effects noted. J. Christopher, 4/11/85.

REPRODUCTION

RAT

016 963648 "Three Generation Reproduction Study in Rats with Alachlor, Final Report (Lasso Technical)". Bio/dynamics, 2/20/81. [BDN-77-422] Alachlor, tech. 0, 3, 10, and 30 mg/kg/day in feed. Originally classified as unacceptable (Dosages not justified and appear to be below the MTD on comparison with dosages tolerated in other long-term studies. Histopathology was not performed on animals which were not successfully bred. Other deficiencies noted.) The 10/29/86 re-examination and rebuttal response led to a re-classification as "acceptable**". Dosage selection was determined to be adequate, however range was lower than currently recommended. The NOEL for parental toxicity is 10 mg/kg/day, based on chronic nephritis in F2b males at 30 mg/kg/day. No apparent reproductive toxicity. The randomization procedure for selection of parental animals, or for the selection of animals to be examined microscopically, was adequate under circumstances of this study. J. Christopher, 4/8/85, C. Aldous, 10/29/86.

099 048634 Monsanto rebuttal to CDFA review of study: 016:963648. Response review and re-evaluation of data by C. Aldous, 10/29/86. See above.

017 963649 Summary of 016:963648.

020 029653 (Previously designated as 963612 or 963612-2). Brief summary of 016:963648.

011 029620 "Summary of Toxicology Studies Conducted on Lasso Herbicide, Chronic and Delayed effects studies: Three-Generation reproduction study with Lasso Technical in albino rats". (Rec. # 963611 given on worksheet. The latter "Rec. #" was not applied uniquely to this study, but was used repeatedly for various types of studies within this review. This study is reported on pp. 12-13 of section C.) IBT, 4/22/74 (BTL-72-12). Summary only. Lasso, tech. An IBT study ruled invalid by EPA. 0, 30, 100, and 300 ppm in diets of "albino" rats. No significant adverse effects noted. UNACCEPTABLE, NOT UPGRADEABLE. (EPA invalid, dose levels apparently too low.) J. Christopher, 4/4/85.

TERATOGENICITY**RAT**

**009 963647 "Teratology Study in rats". (IRDC No. 401-058) 3/21/80. Alachlor, tech. (92.2%). 25 dams/group gavaged with 0, 50, 150, or 400 mg/kg/day. Maternal toxicity NOEL = 150 mg/kg/day (decreased BW gain of pregnant dams, days 6-20, 4 deaths in 400 mg/kg/day group). Developmental toxicity NOEL = 400 mg/kg/day (no apparent effects at HDT). Originally UNACCEPTABLE, now ACCEPTABLE (see response to rebuttal in 102: 048853, 048854, below). J. Christopher, 4/10/85. Rebuttal review by C. Aldous, 10/30/86.

102 048853, 048854 Monsanto rebuttal to J. Christopher review (4/10/85) of 009:963647. New submissions: analysis of test material, surrogate analysis of dosing solution and original dose prep sheets, fetal individual body weight data, necropsy data on dams, reference to a pilot study to determine dosages, clinical observation data, source of male rats given. Additional data is sufficient to warrant upgrade to ACCEPTABLE status. C. Aldous, 10/30/86.

011 029621 (summary of 009:963647, above).

RABBIT

132 067756, " A teratogenicity study in rabbits with Alachlor", (Bio/dynamics, Inc., Study no. BD-87-83, 3/28/88). Alachlor, purity 94.7%, administered by gavage at dose levels of 0 (corn oil), 50, 100 and 150 mg/kg/day from gestation days 7 through 19. There were 18 mated female New Zealand White rabbits/dose. Some reduction in food consumption was observed during the treatment period at each dose level, but body weights were not markedly affected by treatment. Maternal NOEL = 100 mg/kg/day, based on small but statistically significant body weight loss during early treatment period (days 7-10) at 150 mg/kg/day. Developmental NOEL = 150 mg/kg/day (HDT), thus there were **no adverse effects. **Acceptable** (information missing from original CDFA copy of report was provided: see next "one-liner"). (Aldous, 3/17/89 and 3/23/90).

249-132 [missing pages added to original record number = 067756]. Submission contains the pages which were missing from the copy of the report previously submitted to CDFA. These are the Title Page (prepared by Monsanto), Data Confidentiality page, and the GLP Compliance Statement. The original copy evaluated by CDFA contained p. 290 of the report, indicating dates of QA inspections: nevertheless that page did not indicate whether or not there were significant deviations from GLP guidelines. The new submission provided the signed GLP compliance statement, indicating that the study did conform to essential GLP standards. This submission makes the study fully **acceptable**. C. Aldous, 3/23/90.

131 067755 Pilot study for 132:067756, above.

062 006448 "Teratology Study in Rabbits-Technical Alachlor". IRDC, 12/29/83. Alachlor, 94%, administered by gavage to 18 pregnant rabbits/group at 0, 10, 30, and 60 mg/kg/day in mineral oil vehicle. No developmental toxicity nor maternal toxicity observed. UNACCEPTABLE (insufficient dosages, inappropriate vehicle, administration of dosage began 1 day too late) apparently not upgradeable. Rebuttal response below clarified some concerns of original CDFA review, but study is still classified as "unacceptable" (see 101:048851 below). J. Christopher, 4/10/85, C. Aldous, 10/30/85.

101 048851 (with addendum, 101:048852) Monsanto rebuttal to J. Christopher review (4/10/85) of 1983 IRDC rabbit teratogenicity study (062 006448). Registrant provided satisfactory responses to J. Christopher's concerns about the following: analysis of test article, analysis of dosing solution using technical a.i. as the standard, appropriateness of time of dosing, statistical treatments, and presentation of fetal weight data by sex. The issue of adequacy of dosages has not been resolved. Study still not acceptable. Re-evaluation of data by C. Aldous (10/30/85).

012 963645 "Teratology Study in rabbits with Alachlor". IRDC 11/24/80. (IR-79-022) Alachlor, tech. (92.2%). Initially 16 dams/group gavaged with 0, 10, 30, or 60 mg/kg/day in corn oil. 9-14 dams pregnant at term. Insufficient information to fully evaluate, however apparent NOELs for maternal and developmental effects were the HDT = 60 mg/kg/day. UNACCEPTABLE, NOT UPGRADEABLE (too few pregnant dams at term, dosage not justified and apparently below the MTD, no pathology data presented, no clinical observations presented, unacceptable numbers of deaths and abortions in control and treated groups). J. Christopher, 4/9/85.

020 029654 (Old Record No. was 963612-1). Brief summary of 012:963645.

017 963646 Brief summary of 012:963645.

011 029622 "Summary of Toxicology Studies Conducted on Lasso Herbicide, Chronic and Delayed Effects Studies: Teratogenic Study with Lasso Technical in albino rabbits". (Rec. # 963611 given on worksheet.) The latter "Rec. #" was not applied uniquely to this study, but was used repeatedly for various types of studies within this review. This study is reported on pp. 10-11 of section C.) IBT, 8/14/72 (BTL-72-10). Summary only. Lasso, tech. An IBT study ruled invalid by EPA. 0, 10, and 30 mg/kg/day. No significant adverse effects noted. UNACCEPTABLE, NOT upgradeable. (EPA invalid, dose levels apparently too low.) J. Christopher, 4/4/85.

GENE MUTATION

There is one acceptable gene mutation study in mammalian cells on file for technical alachlor with no mutagenicity reported. The studies in bacteria which have been reviewed do not suggest a high potential for gene mutation, although one of several representative metabolites of alachlor is mutagenic in the Ames test, as indicated below (Study 076:17661). CDFA requires mutagenicity studies on the technical material to meet the respective data category requirements, thus study 028:963650 (below) does not fill the gene mutation "data gap", although it is a well-executed study on the analytical grade material. A supplementary information worksheet has been included respecting the change of status.

Earlier versions of the Summary of Toxicology Data indicated a "possible adverse effect" on page 1 for gene mutation based on the study with a metabolite (076:017661). In this study, the mutation frequency was increased greater than 3-fold at 10 mg/plate and also increased at 3.0 mg/plate with Salmonella strain TA100. The other 3 strains tested (TA1535, TA1537, and TA98) were clearly negative at these concentrations. Based on the negative results with technical alachlor in mammalian cells (108:053748) and the negative results in the other reports with bacteria, the positive result with a metabolite in one strain only of Salmonella is of questionable biological significance. Therefore, the weight of evidence is for a lack of activity for gene mutation. C. Aldous and J. Gee, 3/17/89.

Bacterial systems

028 963650 (worksheet incorrectly lists as Rec. # 096350). Institute of Environmental Toxicology (ET 80-0101), Jan., 1980. Alachlor, analytical grade. Ames test with strains TA1538, TA98, TA100, TA1535, and TA1537. Duplicate plates at 10, 50, 100, 500, 1000, and 5000 ug/plate, w/ and w/o S9. Also E. coli WP2 hcr at same treatment levels. All responses negative. Classified as ACCEPTABLE by John P. Christopher, despite use of analytical grade alachlor and despite test apparently having been run only once with duplicate plates. Study now re-classified as UNACCEPTABLE because of the inappropriate grade of test article. See statement at beginning of this section of the summary. Note: EPA One-liner lists this study

as ACCEPTABLE for both the rec-assay and the reverse mutation portions of the report. J. Christopher, 4/5/86.

076 017661 Monsanto, 9/17/84. N-[2-ethyl-6-(1-hydroxyethyl)phenyl]-N-(methoxymethyl)-2-methylsulfonylacetamide. 0, 0.01, 0.04, 0.2, 1.0, 3.0, 10 mg/plate; triplicate plates w/ & w/o S9. Test article represents a class of major alachlor metabolites. Test article mutagenic w/ & w/o S9 (to comparable degree) in TA100 strain. UNACCEPTABLE to fill alachlor GNMU data requirement, however useful data. J. Christopher, 4/8/85.

076 17657 Monsanto, 5/18/84. [N-(2,6-diethyl)phenyl-N-methoxymethyl]-2-amino-2-oxoethanesulfonic acid, sodium salt. 0, 0.01, 0.04, 0.2, 1.0, 3.0, 10 mg/plate; triplicate plates w/ & w/o S9. Test article represents a class of major alachlor metabolites. Test article occasionally elevated revertants/plate to slight extents (signif., $p < 0.05$) with TA100 or TA1537, but elevations were not consistent and did not appear to be biologically significant. UNACCEPTABLE, but useful data. J. Christopher, 4/8/85.

076 025283 (no Rec. # assigned when originally reviewed) Monsanto, 5/18/84. (N-[2,6-diethyl)phenyl]-N-methoxymethyl-2-(hydroxy)acetamide. 0, 0.01, 0.04, 0.2, 1.0, 3.0, 10 mg/plate; triplicate plates w/ & w/o S9. Test article represents a class of major alachlor metabolites. No evidence of mutagenicity. ACCEPTABLE study for this metabolite (does not fill data requirement for tech. a.i.). J. Christopher, 4/8/85.

076 017658 Monsanto, 5/18/84. 3-[N-[2,6-diethyl]phenyl-N-methoxymethyl)-2-amino-2-oxoethane-sulfinyl]-2-hydroxypropanoic acid, sodium salt. 0, 0.01, 0.04, 0.2, 1.0, 3.0, 10 mg/plate; triplicate plates w/ & w/o S9. Test article represents a class of major alachlor metabolites. Test article not mutagenic according to significance criteria established. Study found UNACCEPTABLE due to poor response of strain TA1537 to positive control w/o S9. Acceptability is a moot issue in a supplementary test such as this: useful information was provided, and there is no apparent reason to repeat the test. J. Christopher, 4/8/85.

076 017659 Monsanto, 5/18/84. 2',6'-diethyl-N-[methoxymethyl] oxanilic acid, sodium salt. 0, 0.01, 0.04, 0.2, 1.0, 3.0, 10 mg/plate; triplicate plates w/ & w/o S9. Test article represents a class of major alachlor metabolites. Test article not mutagenic. Study found UNACCEPTABLE due to poor response of strains TA1537 and TA98 to positive control w/o S9. Acceptability is a moot issue in a supplementary test such as this: useful information was provided, and there is no apparent reason to repeat the test. J. Christopher, 4/8/85.

076 017660 Monsanto, 2/22/85. Introduction to the several gene mutation studies of compounds representative of major alachlor metabolites: Reports contained in same volume: see above one-liners.

028 963653 Publ., Northern Illinois Univ., 1981. Alachlor mixed with other pesticides in various combinations. Ames test. No data. No adverse effects indicated. UNACCEPTABLE (not tech. material, no data). J. Christopher, 4/5/85.

028 963652 (worksheet incorrectly lists as Rec. # of 96352). (Inst. of Environmental Toxicology, Japan; Mut. Res. 40:19-30, 1976) Alachlor, grade not specified. Reversion assays with E. coli (WP2) and S. typhimurium (Ames series). No activation. No data presented. No adverse effects reported. UNACCEPTABLE (test article not characterized, no data). J. Christopher, 4/5/86.

028 963651 Publ., Lilly Research Labs, 1981. Alachlor, grade not specified. Tested for both modified Ames test (with and without activation) and in vitro rat hepatocyte UDS assay. No adverse effects reported. UNACCEPTABLE (no data, no detail of experimental methods, etc.). J. Christopher, 4/5/85.

011 033212 (Rec. # 963611 given on worksheet. The latter "Rec. #" was not applied uniquely to this study, but was used repeatedly for various types of studies within this review. This study is on pp. 19-20 of section C.) IBT (BTL-75-144A). Study validated by EPA. Summary only. Presume tech. alachlor (CP-50144, 92.6%). Host-mediated mutation assay with S. typhimurium (strain G 46) in rats. No mutagenicity observed. UNACCEPTABLE. NOT upgradeable.

Summary only. Insufficient data for independent evaluation. Unlikely that investigators could demonstrate that treatment was performed to the limits of toxicity of test organism (i.e., the bacterium). J. Christopher, 4/4/85.

011 029617 An invalid IBT bacterial reverse mutation study.

011 029616 An valid IBT host-mediated assay with *S. typhimurium* strain G 46 injected into mice. No data presented, no adverse effects reported.

Mammalian systems

** 108 053748 "CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay". (Pharmakon, 7/30/84, PK-83-249, Study No. 314-MO-006-83) Alachlor technical, 95.4%; CHO/HGPRT assay, tested with and without rat liver activation; S9 at 2% or 5%, 0, 15, 30, 60, 100, 150, 200 or 330 ug/ml, 5 hour incubation; 8-day expression for thioguanine resistance; no increase in mutation frequency reported; acceptable. J. Gee, 3/12/87.

CHROMOSOME

** 054 006437 Hazleton Labs, 3/1/84. "In vivo bone marrow chromosome study in rats". Rats dosed with tech. alachlor by gavage in corn oil: 0, 100, 330, and 1000 mg/kg in a single administration. Rats killed at 6, 12, 24, and 48 hr after dosing (48-hr specimens not read as there was no evidence of mitotic delay). No increase in aberrations noted. Study classified as unacceptable by J. Christopher, due principally to lack of evidence that the high dose was maximized. (see rebuttal response, below). Reconsideration by Gee, in light of the submission of study on absorption in rats following oral dosing (109:054066), found that the high dose of 1000 mg/kg was reasonable based on efficient absorption and on closeness of dose levels to the LD50 in rats. Report is now **acceptable**. J. Christopher, 4/5/86, C. Aldous, 10/29/86, J. Gee, 3/13/87.

EPA one-liner: UNACCEPTABLE [No evidence presented of systemic absorption and/or transport to target tissue (bone marrow)]. (1-liner dated 11/13/84)

100 048635 Monsanto rebuttal to 4/5/86 J. Christopher review of 054:006437. This review still did not find report acceptable, due to lack of evidence that the high dose was sufficiently high. C. Aldous, 10/29/86.

109 054066 Supplement to 054:006437 and the basis of the decision to upgrade the study to acceptable. "A Mechanistic Study of the Interaction of Alachlor with Blood, Part I., Distribution of Alachlor in Blood Components after Oral and Dermal Dosing in the Rat". (Monsanto, 1/29/85) Male rats were dosed with a single oral dose of 7.44 or 780 mg/kg of 14-C-labeled Alachlor. Blood samples were taken at several intervals over 48 hours and the distribution of the radioactivity in plasma and blood cells measured. Excretion in the urine was also followed. The blood level was maximal at 6 to 24 hours. This was taken as evidence that the alachlor was absorbed rapidly and the blood level was maintained over a significant period of time during which marrow cells would be exposed, in response to the deficiency noted by EPA. J. Gee, 3/13/87.

011 033209 (Rec. # 963611 given on worksheet. The latter "Rec. #" was not applied uniquely to this study, but was used repeatedly for various types of studies within this review. This study is reported on p. 17 of section C.) IBT, 7/26/72 (BTL-72-11). Dominant lethal, mouse. Summary only. Presume tech. alachlor (CP-50144, 92.6%). An IBT study ruled valid by EPA. Single ip injection of 15 or 30 mg/kg, males mated over 6-week period. No mutagenic response reported. UNACCEPTABLE, NOT UPGRADEABLE. (Summary only, no justification of dosage levels, no evidence that dosages were maximized.) J. Christopher, 4/4/85.

DNA DAMAGE

****054 006438** SRI, 4/5/84. In vivo rat hepatocyte UDS assay. Alachlor, tech. 6 rats/dose gavaged with 50, 200, and 1000 mg/kg: 3 rats sacrificed at 2 hr, 3 at 12 hr in each group.

Two rats each for pos. and neg. controls, killed at 12 hr. Alachlor found to be weakly genotoxic in this assay (significant increase in UDS in 1000 mg/kg group sacrificed after 12 hr). ACCEPTABLE. J. Christopher, 4/5/85.

EPA one-liner: ACCEPTABLE (Positive for UDS at the HDT....1000 mg/kg).

028 000995 (worksheet incorrectly lists as Rec. # of 96350; part of report in Vol. -028, part C. Balance of report is under GNMU, 028/963650). (Inst. of Environmental Toxicology, Japan; 1/80) Alachlor, analytical grade. B. subtilis rec assay. 20, 100, 200, 500, 1000, and 2000 ug/disk. Single rep only. No apparent DNA damage. UNACCEPTABLE to fill DNA damage data gap, NOT upgradeable: Single rep not acceptable, technical material not used. EPA One-liner lists this study as acceptable. J. Christopher, 4/5/86.

011 033210 IBT-invalid recombination assay (BTL-75-142, 4/20/76). No adverse effects indicated.

028 046944 (worksheet incorrectly lists as Rec. # of 96352). (Inst. of Environmental Toxicology, Japan; Mut. Res. 40:19-30, 1976) Alachlor, grade not specified. rec-assay with Bacillus subtilis. Apparently a single plate, at one concentration of test article. No activation. No data presented. No adverse effects reported. UNACCEPTABLE (test article not characterized, no data). J. Christopher, 4/5/86.